REMARKS

Favorable consideration and allowance are respectfully requested for currently pending claims 1-28 in view of the foregoing amendments and following remarks.

Claim 1 is amended to recite that the two active substances are present in separate subunits so as to not impair the release profiles of the two active substances. Support for this change may be found in the specification as originally filed, for instance, at least in paragraphs [0008] and [0009] on page 2. Claims 1 and 2 are also amended to spell "pharmaceutically" correctly.

The rejection of claims 1-28 on the ground of nonstatutory obviousness-type double patenting over claims 1-12, 16-23, 41 and 42 of U.S. Patent No. 6,558,701 (the '701 patent) is respectfully traversed. Applicants are filing a Terminal Disclaimer simultaneously with this amendment, rendering this rejection is moot. Withdrawal of the rejection is therefore respectfully requested.

The rejection of claims 1-28 under 35 U.S.C. § 103(a) over Raffa (EP 0 546 676 A1) in view of Oshlack *et al.* (6,077,533) is respectfully traversed.

The presently claimed invention relates to an oral administration unit containing the active substances tramadol and diclofenac and/or their respective physiologically compatible salts. Each of the two active substances is present in subunits which are separately formulated in each case, while they are provided in the same larger administration unit (see paragraph [0002] of the publication of the present application). This formulation provides a new pharmaceutical dosage form for the combined administration of tramadol and diclofenac.

Together, tramadol hydrochloride and diclofenac sodium form a sparingly soluble compound. This sparing soluble compound reduces the bioavailability of the two active substances so that higher dosages are required to compensate for the impaired solubility and achieve commensurate physiological effectiveness (see the present specification, page 2, paragraph [0006]).

The present inventors surprisingly discovered that they could avoid the reduced bioavailability problems with an oral administration unit comprising a first active substance tramadol or a pharmaceutically acceptable salt thereof, and a second active substance diclofenac or a pharmaceutically acceptable salt thereof, wherein the two active substances are present in separate subunits (see present application, paragraph [0009]). As indicated previously, Figures 1-4 of the present application demonstrate that (a) the inventive oral administration unit (Figures 1 of the present application) displays an improved release profile compared to a conventional matrix tablet (Figure 2 of the present application); (b) the oral administration unit comprising both active substances displays a sigmoidal release profile for tramadol as well as for diclofenac – this is commonly only achieved with retard pellets having only one of the active substances (see Figures 1, 3 and 4 of the present application); and (c) the release rate of the active substances from the inventive oral administration unit is comparable to that of the retard pellets comprising only one active substance, i.e. either tramadol or diclofenac (see, Figures 1, 3 and 4 of the present application).

This evidence, showing that both active substances, diclofenac and tramadol, display a sigmoidal release profile from the oral administration unit of the invention, which is almost identical to the release profiles measured for the pellets containing a single active substance, i.e., either tramadol or diclofenac, proves that the inventive oral administration unit does not impair the release profiles of the two active substances.

In contrast, as can be seen from Figure 2, if tramadol-HCl and diclofenac-Na are embedded together in a conventional matrix tablet, the release profile of both active substances is disadvantageous.

The Raffa reference relates to a composition comprising a tramadol material and an NSAID. Raffa does not explicitly disclose the presently claimed combination of tramadol or a pharmaceutically acceptable salt thereof with diclofenac or a pharmaceutically salt thereof. Moreover, Raffa provides no

indication that there might be any problem arising from the direct combination of tramadol and diclofenac.

Oshlack discloses sustained release oral solid dosage forms of opioid analgesics provided as multiparticulate systems containing pharmaceutically acceptable inert beads which are powder layered with therapeutically active agents. Oshlack does not disclose the presently claimed combination of tramadol and diclofenac nor the problem arising from the direct combination of these two active substances.

Considering the disclosures of Oshlack and Raffa, one of ordinary skill in the art would have no reason to arrive at the presently claimed invention, where tramadol and diclofenac (or salts thereof) are provided in separate subunits of a an oral administation unit. Rather, the proposed combination of these two references and the modifications of these references necessary to arrive at the claimed invention is based purely on hindsight, relying on the present claims as a roadmap to identify the different parts of the claims.

As pointed out by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 SCt 1727, 82 USPQ2d 1385, 1396 (U.S. 2007):

> [R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". (Quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329 (Fed. Cir. 2006) with approval).

Although an explicit teaching, suggestion or motivation need not be found in the cited references, to properly reject for obviousness, it is nevertheless necessary for the Examiner to articulate a convincing rationale as to what would lead a person skilled in the art to depart from the teachings of the prior art and strike out in the new direction claimed by applicants as their invention. In the present instance, the Office Action offers no persuasive rationale to explain why the skilled artisan would depart from the teachings of Raffa and try to include the teachings of Oshlack. Similarly, even if the skilled artisan were to try to combine these references the skilled artisan would have no reason to combine a

subunit dosage form of tramadol with a subunit dosage form of diclofenac so as to not impair the release profiles of the two active substances.

When Raffa considers diclofenac or a pharmaceutically acceptable salt thereof as a possible active ingredient, it does so only in an extensive list of NSAIDs (see Raffa, page 3, line 50 to page 4, line 15). Raffa fails to describe any potential solubility problem associated with the combination of tramadol and diclofenac. The Office Action admits that Oshlack does not teach the combination of tramadol and diclofenac. Indeed, as indicated previously, Oshlack does not describe an oral dosage form where two active ingredients are provided, much less a dosage form where two active ingredients are provided in separate subunits. Instead, Oshlack describes formulations with the *same* active ingredient provided in different forms.

Thus, if one of skill in the art were, for some reason, to ignore Oshlack's description of single active ingredient dosage forms and try to combine tramadol with an NSAID in a dosage form as described in Oshlack, given Raffa's description of synergies between tramadol and NSAID's the person of skill in the art would be inclined to provide a combination of tramadol and NSAID together and spray this combination onto a single batch of beads. Thus, not only is there is nothing to cause one of skill in the art to go to the trouble of providing the tramadol and NSAID apart in separate subunits, as is required of the present claims, but instead, the art actually teaches away from such a formulation, so as to achieve the synergies Raffa describes.

Accordingly, cited references, whether considered together or alone, fail to describe a formulation where **different** active ingredients are provided in **separate** subunits, much less a formulation where tramadol and diclofenac are the active ingredients in these separate subunits. Indeed, the skilled artisan would have no reason to combine these references and then go to the added trouble involved with disregarding the references and deciding for some reason to separate the active ingredients within the formulation.

As a result, it follows that a proper, *prima facie* case of obviousness has not been made out, and reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket No. 029310.50777CP).

Respectfully submitted,

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/Christopher T. McWhinney/
Christopher T. McWhinney
Registration No. 42,875

J. D. Evans
Registration No. 26,269

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
JDE:CTM (4889373)